REMARKS

PRIORITY

The Examiner has stated that claims 1-10, 13, 18-20, 23, 25-26, 29, 31-33 and 36 may not have the benefit of the filing date of the parent application serial number 08/263,923, filed on 06/21/94, issued as U.S. patent no. 5,679,582 ("the '582 patent), because the method for screening 'more than 1000 compounds or excess of one thousand test ligands in a single day' claimed in these claims has allegedly no clear support in the parent application. Accordingly, the Examiner has stated that the effective filing date for these claims is 10/25/95.

Applicants respectfully submit that these claims have been cancelled. Newly submitted claims 66-74, 77, 82-84, 87, 89-90, 93, 95-97, 100 and 102-107, which are directed to "rapid, high throughput methods", have the benefit of the 06/21/1994 filing date of the '582 patent. Adequate support for these claims is found in the specification of the '582 patent, as well as in the Judge's opinion (*See Scriptgen Pharmaceuticals, Inc. v. 3-Dimensional Pharmaceuticals, Inc., Civil Action No. 98-583-GMS*) on allegations of infringement of two U.S. patents: 5,585,277 and the '582 patent.

For instance, the specification of the '582 patent clearly states, particularly on page 2, lines 17-19:

> There is a need in the art for a rapid, cost-effective, high-throughput assay that enables the screening of large numbers of compounds for their ability to bind therapeutically or physiologically relevant proteins.

On page 10, line 17 to page 11, line 2:

> For the purpose of high-throughput screening, the experimental conditions described above are adjusted to achieve a threshold proportion of test ligands identified as "positive" compounds or ligands from among the total compounds screened. This threshold is set according to two criteria. First, the number of positive compounds should be managed in practical terms. Second, the number of positive compounds should reflect ligands with an appropriable affinity towards the target proteins. A preferred threshold is achieved when 0.1% to 1% of the total test ligands are shown to be ligands of a given target protein.

On page 11, lines 16-18:

> The present invention can be applied to large-scale systematic high throughput procedures that allow a cost-effective screening of many thousands of test ligands.

Thus, as set forth in the specification of the '582 patent, a high throughput assay or large scale, systematic high throughput screen involves testing enough compounds so that 0.1% to 1% of the total number of compounds are identified as hits, with an appreciable affinity towards the target proteins. In Example 9, the high throughput screening involves testing 3,600 compounds, of which 24 were identified as ligands (*See* specification page 36, lines 6-9). In Example 10, 4,000 compounds were screened, of which 23 were identified as ligands (*See* specification page 39, lines 9-11).

In addition, as Judge Slate pointed out that the term "rapid, large scale screening .... means that several thousand test ligands are to be screened through a process which can be completed within a number of hours...." Thus, the specification of the '582 patent discloses screening methods which are rapid and large-scale.

Accordingly, since the specification of the '582 patent clearly support the "rapid, large-scale, high throughput methods" as claimed in the newly submitted claims, Applicants respectfully submit that the effective filing date for these claims is 6/14/1994.

THE AMENDMENTS

Applicants cancel all pending claims 1-65, and add new claims 66 to 107. These new claims add no new subject matter and are fully supported throughout the specification and the claims as filed. Support and reasoning for the amendments are provided below.

Support for New Claims and Reasons for Amendments

These amendments are made to clarify the claims in order to expedite allowance of the present application. Applicants reserve the right to file related applications including claims cancelled or withdrawn in this or other related applications. These claims make cosmetic changes and add no new subject matter and are fully supported throughout the specification, including the drawings and the claims as originally filed.

For instance, new independent claim 66, based on cancelled claim 1, includes the same subject matter as originally claimed, and is simply amended to better clarify the invention. The term "a drug screening method" in the preamble of the claim 66 is replaced by "a ligand screening method" for the consistency of use of the term "ligand" throughout the entire claim. The term "ligand" is clearly defined in the specification, particularly on page 5, lines 1-18.

In addition, the steps (e), (f) and (g) in independent claim 66 and (e), (f), (g) and (h) in independent claims 67, 68, 75, 76 and 80 are supported in the specification, for example, on page 3, lines 1-10, page 7, lines 15-20, and page 8, line 19 to page 9, line 7.

The claims are definite under 35 U.S.C. 112, second paragraph.

In regard to claim 1, the examiner alleges that it is unclear whether "the ligand" in the claimed method is "the drug". Applicants have cancelled this claim, and new independent claim 66 replaces the term "a drug screening method" with "a ligand screening method". The change has been made merely to clarify the claim.

In addition, the Examiner alleges that "the instant claimed method does not have any method steps in which drug or drugs are screening." Applicants have cancelled the claim, and the rejection is not applicable to new claim 66 because it explicitly recites step (g) as "repeating steps (b) to (f) with more than one thousand of selected ligands until ligands that bind to said target protein are identified".

Moreover, the Examiner alleges that it is unclear "what is the end result of the method steps, if ligand which are known to bind to the target are selected prior to the claimed method." Applicants have cancelled the claim, and respectfully submit that the Examiner has misunderstood the invention. In an effort to advice prosecution, Applicants have added new claim 66 explicitly reciting that "selecting a plurality of ligands not known to bind to target protein."

Furthermore, the Examiner alleges that it is unclear "which one of the selected plurality of test ligands is incubated with the target step b).... and how and/or which the test ligand is selected from the plurality of test ligands...". Applicants have cancelled this claim, and respectfully submit that the rejection is not applicable to new claim 66 because it clearly recites

in step b) that "incubating in an assay one selected ligand....". Steps (c) through (g) clearly indicate how and/or which the test ligand is selected.

Accordingly, Applicants assert that the claims are definite, and respectfully requests that the rejection be withdrawn.

In regard to claims 1-37, step c), the Examiner alleges that it is unclear "whether the test ligand in step b) is same as the test ligand in step c)." Applicants have cancelled these claims, and respectfully submit that the rejection is not applicable to new claims 66-102 because these claims clearly indicate that the test ligand in step b) is the same as the test ligand in step c), providing "said selected ligands", rather than "a test ligand" is used in step c). Applicants respectfully request that the rejection be withdrawn.

In regard to claims 1-10, 13, and 16-37, the Examiner alleges that "the claimed methods are interpreted as a single assay method which is repeated a number of times.... and not a single high throughput assay in which a plurality of compounds are tested in a single assay." Applicants have cancelled these claims. Claims 1-10 are replaced by claims 66-74 and 102; claim 13 is replaced by claim 77, and claims 16-37 are replaced by claims 80-101. Applicants respectfully submit that the Examiner has misunderstood the claimed invention, which refers to the rapid, large-scale high throughput screening methods. The independent claims 66, 67, 68, 75, 76 and 80 explicitly recite steps (a) through (g) and (h) engaged in a single highthroughput screen assay. Accordingly, Applicants respectfully request that the rejection be withdrawn.

In regard to claims 1-30, the Examiner alleges that "the instant claims do not recite how the extent of the folded or unfolded state of the target protein in test combination and control combination are measured". Applicants have cancelled these claims, and respectfully submit that the rejection is not applicable to new claims 66-94 and 102 because the independent claims 66, 67, 68, 75, 76 and 80 explicitly recite steps (d) through (f), explaining how the extent of the folded or unfolded state of the target protein in test combination and control combination are measured. Accordingly, Applicants respectfully request that the rejection be withdrawn.

In regard to claim 2, the Examiner alleges that "it is unclear at the end of the claimed method which of the test ligands bind to the target protein are identified or selected... and what is the relationship between the test ligands which bind to the target protein and the lead

compound." Applicants have cancelled this claim, and respectfully submit that the rejection is not applicable to new claim 67 because the term "ligand" is replaced with the term "compound", and new claim 67 explicitly recite step (h) as "selecting as a lead compound any selected compound in a test combination in which said target protein is present in the folded state to a greater extent in the test combination than in the control combination." Accordingly, Applicants respectfully request that the rejection be withdrawn.

In regard to claim 4, the Examiner alleges that claims 4 lacks proper antecedent basis for the term "said selected ligands", and it is unclear "how to identify from the selected ligands which would be pharmaceuticals". Applicants have cancelled this claim. The new claims 102-107 provide proper antecedent basis for the term "said selected compound", thus, rendering the rejection moot. In addition, the new claims 102-107 explicitly recite "...identifying at least one each of said selected compound for possible development as a pharmaceutical by further determination of pharmacological characteristics of said selected compound." Accordingly, Applicants respectfully request that the rejection be withdrawn.

In regard to claims 5 and 25-30, the Examiner alleges that the term "small" is indefinite, and requires that the size of the organic molecule is recited in the claims. Applicants have cancelled these claims, and replaced them with claims 69 and 89-94. Applicants respectfully disagree with the Examiner's allegation. The term "small organic molecule" has ordinary meaning to one skilled in the art, and therefore, set forth the meets and bounds of the claimed invention. Accordingly, Applicants respectfully request that the rejection be withdrawn.

In regard to claim 16, the Examiner alleges that "it is unclear at the end of the claimed method which of the test ligands that bind to the target protein are identified." Applicants have cancelled this claim, and replaced it with claim 80. The rejection is not applicable to the new claim 80 because it explicitly recites "selecting as a lead compound any selected compound in a test combination in which the target protein is present in the folded state to a greater extent than in the control combination." Accordingly, Applicants respectfully request that the rejection be withdrawn.

In regard to claims 18-24, the Examiner alleges that the control combination is subjected to different conditions. Applicants have cancelled these claims, and replaced them with new

claims 82 through 88. The new claims 82-88 have deleted the term "said control combination", providing the conditions for test combination and control combination, thus, rendering the rejection moot.

In regard to claims 31-37, the Examiner alleges that the claimed method "no where teaches a use of a fluorescence probe or tag such that the fluorescence of the compound is measured." Applicants have cancelled these claims, and replaced them with new claims 95-101. The new claims 95-101 explicitly recite "... measuring the extent to which said target protein is unfolded in each of said test combination and said control combination using fluorescence spectroscopy by contacting said test combination and said control combination with a fluorescence probe, rendering the rejection moot. Accordingly, Applicants respectfully request that the rejection be withdrawn.

The claims are novel under 35 U.S.C. 102(a).

The examiner has rejected claims 11-12, 14-17, 21-22, 24, 27-28, 30, 34-35, and 37 as allegedly being anticipated by Volkin, et al. (Harnessing Biotechnology for the 21st century, pages 298-302, August 1992). Applicants have cancelled these claims and submitted new claims 75-76, 78-81, 85-86, 88, 91-92, 94, 98-99 and 101, where independent claims 75-76 are based on cancelled independent claims 11-12; claims 78-81 are based on cancelled claims 14-17; claims 85-86 are based on cancelled claims 21-22; claim 88 is based on cancelled claim 24; claims 91-92 are based on cancelled claims 27-28; claim 94 is based on cancelled 30; claims 98-99 are based on cancelled claims 34-35; and claim 101 is based on cancelled claim 37. Newly submitted independent claims 75-76 and 80 are drawn to high throughput screening a plurality of compounds and to identify lead pharmaceutical compounds from among a plurality of compounds not known to bind to the target. Such limitation is not disclosed in Volkin et al.

Volkin et al. described studies of stabilization of acidic fibroblast growth factor (aFGF) in the presence of specific and non-specific polyanionic compounds already known or expected to bind aFGF. The low throughput studies described in this reference in no way correspond to the high throughput screening assays for first pass identification of lead pharmaceutical compounds from among a plurality of compounds not known to bind to the target.

In particular, Volkin reference discloses experiments that examine the influence of heparin, heparin fragments, chemically-modified heparin, polyanions, and phosphorylated inositols on the thermal stability of aFGF as measured by fluorescent spectroscopy. The repetition of 20 individual experiments (as set forth in Table 1 of Volkin) does not constitute, a rapid high throughput screening method for a large number of compounds. Rather, a rapid method for screening potential ligands would involve an approach in which a large number of ligands were screened, essentially simulataneously within a matter of hours, even minutes. The approach taken by Volkin of individual repetition of an experiment for each ligand does not, therefore, constitute or suggest a rapid screening method. The experiments performed by Volkin do not constitute large-scales or rapid screening, as set forth in the specification and the claims.

Furthermore, the compounds tested for their effect on the thermal stability of aFGF in the Volkin reference were known or expected to bind aFGF. The following list summarizes these compounds.

a. *heparin*: previously known to bind to aFGF (Burgess and Maciag, 1989, Ann. Rev. Biochem, 58:575-606);

b. *disaccharide*: previous known not to bind to aFGF (Barzu et al., 1989, Cell Physiol. 140(3):538-46;

c. *tetrasaccharide*: previously known to bind aFGF (Zhou et al., 1992, Heparin and Related Polysaccharides, Edited by D.A. Lane et al., Plenum Press, New York);

d. *hexasaccharide*: previously known to bind to aFGF (Barzu et al., 1992, Heparin-derived Oligosaccharides: Affinity for Acidic Fibroblast Growth Factor and Effect on its Growth-Promoting Activity for Human Endothelial Cells, Edited by D.A. Lane et al., Plenum Press, New York).

e. *octasaccharide*: previously known to bind to aFGF (Barzu et al., 1989, J. Cell. Physiol. 140(3):538-46; Zhou et al., 1992, Heparin and Related Polysaccharides, Edited by D.A. Lane et al., Plenum Press, New York).

f. decasaccharide: previously known to bind aFGF (Barzu et al., 1989, J. Cell. Physiol. 140(3):538-46; Zhou et al., 1992, Heparin and Related Polysaccharides, Edited by D.A. Lane et al., Plenum Press, New York).

g. *low molecular weight heparin*: previously known to bind to aFGF (Copeland et al., 1991, Arch. Biochem. Biophys., 289:53-61).

h. *desulfated heparin*: previously known to bind to aFGF (Belford et al., 1992, Biochemistry, 31(28):6498-503).

i. *partially desulfated heparin*: previously known to bind to aFGF (Belford et al., 1992, Biochemistry, 31(28):6498-503).

j. *epoxy-heparin*: as a heparin compound, expected to bind aFGF.

k. *sulfated β-cyclodextrin*: demonstrated to bind to aFGF with suramin competitive binding assay prior to thermal denaturation experiments.

l. *sucrose octasulfate*: as a polyanion, expected to bind aFGF.

m. Inositol hexasulfate: demonstrated to bind to aFGF with suramin competitive binding assay prior to thermal denaturation experiments. Also previously known to bind to aFGF (Dabora et al., 1991, J. Biol. Chem., 266(35):23637-23640).

n. Phytic acid: demonstrated to bind to aFGF with suramin competitive binding assay prior to thermal denaturation experiments.

o. Tetrapolyphosphate: as a polyanion, excepted to bind aFGF.

p. Phosphorylated inositol: previously known not to bind to aFGF (Dabora et al., 1991, J. Biol. Chem., 266(35):23637-23640). Dabora et al. disclosed that only inositol polyphosphates stabilize aFGF, therefore singularly phosphorylated inositol was known not to stabilize, and not to bind, aFGF.

q. Diphosphorylated inositol: previously known to bind to aFGF (Dabora et al., 1991, J. Biol. Chem., 266(35):23637-2364).

r. Triphosphorylated inositol: previously known to bind to aFGF (Dabora et al., 1991, J. Biol. Chem., 266(35):23637-2364).

s. Tetraphosphorylated inositol: previously known to bind to aFGF (Dabora et al., 1991, J. Biol. Chem., 266(35):23637-2364).

t. Hexaphosphorylated inositol: demonstrated to bind to aFGF with suramin competitive binding assay prior to thermal denaturation experiments. Also previously known to bind to aFGF (Dabora et al., 1991, J. Biol. Chem., 266(35):23637-2364).

Thus, Volkin et al. do not disclose the claimed invention: testing a plurality of ligands and high throughput screening assays for identification of lead pharmaceutical compounds from among a plurality of compounds not known to bind to the target protein. Applicants respectfully request that the rejection be withdrawn.

The claims are novel under 35 U.S.C. 102(a).

The examiner has rejected claims 11-12, 14-17, 21-22, 24, 27-28, 30, 34-35, and 37 as allegedly being anticipated by Tsai et al. (pharmaceutical Research, vol. 10, May 1993, pages 649-659). As stated above, Applicants have cancelled these claims and submitted new claims 75-76, 78-81, 85-86, 88, 91-92, 94, 98-99 and 101. Newly submitted independent claims 75-76 and 80 are drawn to high throughput screening a plurality of compounds and to identify lead pharmaceutical compounds from among a plurality of compounds not known to bind to the target. Such limitation is not disclosed in Tsai et al.

The Tsai reference describes measuring the effects of a number of compounds; again, these compounds were tested over a long period of time. They do not constitute a plurality or large number of compounds, as contemplated by the application (how do twenty or so compounds yield 0.1%, or even 1%, leads?). Furthermore, many of the compounds tested in the Tsai reference are non-specific stabilizers, such as sodium sulfite, dextrose, sorbitol, trehalose, EDTA, sucrose, glycerol, xylitol, manitol, CHAPS, β-mercaptoethanol, dithiothreitol, and the like. These compounds are generally formulary not pharmaceuticals. Finally, to the extent that there is specific binding occurring, the compounds would be known to or expected to bind, as described with respect to the Volkin reference.

Thus, Tsai et al. do not disclose the claimed invention: testing a plurality of ligands and high throughput screening assays for identification of lead pharmaceutical compounds from among a plurality of compounds not known to bind to the target protein. Applicants respectfully request that the rejection be withdrawn.

The claims are nonobvious under 35 U.S.C. 103(a).

The examiner has rejected claims 1-10, 13, 18-20, 23, 25-26, 29, 31-33 and 36 as being obvious over Volkin, et al., (Harnessing Biotechnology for the 21st century, pages 298-302, August 1992) and Agrafiotis et al (U.S. Patent 5,436,564, "the '564 patent). Applicants have

cancelled these claims and submitted new claims 66-74, 77, 82-84, 87, 89-90, 93, 95-97, 100 and 102-107, where newly submitted claims 66-74 are based on cancelled claims 1-10; new claim 77 is based on cancelled claim 13; new claims 82-84 are based on cancelled claims 18-20; new claim 87 is based on cancelled claim 23; new claims 89-90 are based on cancelled claims 25-26; new claim 93 is based on cancelled claim 29; new claims 95-97 are based on cancelled claim 31-33; new claim 100 is based on cancelled claim 36 and new claims 102-107 are based on cancelled claim 4. Newly submitted independent claims 66, 67 and 68 are drawn to a ligand screening method for identifying lead pharmaceutical compounds by screening a plurality of test compounds not known to bind to the target proteins and high throughput screening assays.

Applicants assert that the Volkin reference does not disclose all the elements of the claimed invention. In particular, as detailed immediately above, Volkin, et al., does not disclose testing a plurality of ligands and high throughput screening assays for identification of lead pharmaceutical compounds from among a plurality of compounds not known to bind to the target protein. Moreover, as discussed above, Applicants respectfully submit that the effective filing date for these claims is 06/14/1994, which is earlier than the filing date of the Afrafiotis reference. Therefore, the Afrafiotis is not prior art.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

The claims are nonobvious under 35 U.S.C. 103(a).

Furthermore, the examiner has rejected claims 1-10, 13, 18-20, 23, 25-26, 29, 31-33 and 36 as being obvious over Tsai et al., (Pharmaceutical Research, vol. 10, May 1993, Pages 649-659) and Agrafiotis et al (U.S. Patent 5,436,564, "the '564 patent). Applicants have cancelled these claims and submitted new claims 66-74, 77, 82-84, 87, 89-90, 93, 95-97, 100 and 102-107. As indicated immediately above, newly submitted independent claims 66, 67 and 68 are drawn to a ligand screening method for identifying lead pharmaceutical compounds by screening a plurality of test compounds not known to bind to the target proteins and high throughput screening assays.

Applicants assert that the Tsai reference does not disclose all the elements of the claimed invention. In particular, as detailed immediately above, the Tsai reference does not disclose testing a plurality of ligands and high throughput screening assays for identification of lead

pharmaceutical compounds from among a plurality of compounds not known to bind to the target protein. Moreover, as discussed above, Applicants respectfully submit that the effective filing date for these claims is 06/14/1994, which is earlier than the filing date of the Afrafiotis reference. Therefore, the Afrafiotis is not prior art.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

THE JUDICIALLY CREATED DOCTRINE OF OBVIOUSNESS-TYPE DOUBLE PATENTING

The Examiner has rejected claims 1-37 under the judiciary created doctrine of obviousness-type double patenting as being unpatentable over claims 1-47 of U.S. Patent No. 5,679,582 ("the '582 patent"); and over claims 1-17 of U.S. Patent No. 5,587,277 ("the '277 patent"). Claims 1-37 have been cancelled. Applicants respectfully request that the Examiner hold in abeyance the request for a terminal disclaimer for newly submitted claims until allowable subject matter has been established.

CONCLUSION:

Applicants respectfully submit that the claims are ready for examination and in condition for allowance.

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Respectfully submitted,

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In the event this paper is deemed not timely filed the applicants hereby petition for an appropriate extension of time. The fee for this extension may be charged to Deposit Account No.501321 along with any other additional fees that may be required with respect to this paper; any overpayment should be credited to the account. If any fees charged to this Deposit Account will exceed $500, applicant respectfully requests that its counsel be notified of such amounts before the Deposit Account is charged.